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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

HINES, JANA A

ART UNIT	PAPER NUMBER
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1645

DATE MAILED: 10/10/2003

11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/868,753

Applicant(s)

MURPHY ET AL.

Examiner

Ja-Na A Hines

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-19 and 26 is/are pending in the application.
- 4a) Of the above claim(s) 20-25 and 27-32 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-19 and 26 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

SUPPLEMENTAL DETAILED ACTION

Office Action Vacated

1. Applicant's request for vacating the last Office Action is persuasive and therefore, that action is withdrawn.

Election/Restrictions

2. Applicant's election with traverse of Group I in Paper No. 8 is acknowledged. The traversal is on the ground(s) that the claims in groups III and IV should be rejoined with group I because applicant believes they share the same technical feature. This is not found persuasive because the compositions recited in group I can be used with methods other than those recited in groups III or IV. Therefore, the composition's special technical feature is comprised within the composition and not within the methods; therefore the groups lack the same or corresponding technical feature.

The other groups are drawn to unrelated inventions because they are drawn to different uses, functions and effects, thus they are patentably distinct in comparison to the other groups. These special technical features are comprised within their structural differences of the DNA and in the special technical features of the composition or method claims. Accordingly, the groups lack a corresponding technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Drawings

3. Figures 1,2 and 3 refer to sequences without sequence identifying numbers being described within the figure itself or the brief description of the drawings within the specification. Therefore, appropriate correction is requested.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code on at least pages 10 and 13. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.
5. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Sequence Compliance

6. This application on page 18 contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In particular, claim 1 is drawn to a composition comprising a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier. The dependent claims are drawn to the prokaryote being specific bacterial species and that the sequence encodes a diphtheria toxin repressor or IdeR or SirR repressor. Similarly, claim 26 is drawn to a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier. The dependent claims are drawn to the prokaryote being specific bacterial species and that the sequence encodes a diphtheria toxin repressor or IdeR or SirR repressor.

The specification does not provide evidence that all prokaryotes can be comprised within the claimed composition. The specification at pages 7 and 8 refer to preferred prokaryotes being gram positive bacterial species, in particular *Streptococcus* species, *Staphylococcus* species, *Mycobacterium* species, *Actinomyces* species, and only the *Listeria monocytogenes*, *Propionibacterium acnes* and *Erysipelothrix rhusiopathiae* species. Moreover, it is noted that the instant examples are either drawn compositions drawn to *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) or the *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) itself. The specification fails to teach the identity of other prokaryotes, such as any species of blue-green algae. The specification does not state structural characteristics that a prokaryote would need to qualify as a prokaryote capable of comprising the repressor protein. Moreover, there is evidence that other prokaryotic species have not yet been identified and/or classified as capable of comprising the claimed subject matter. In view of the lack of evidence, it is apparent that Applicants were not in possession of additional prokaryotic strains, at the time of filing the instant application.

With the exception of a composition comprising *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) or the *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) itself, the skilled artisan cannot envision the detailed structure of the composition or the virulent or opportunistic prokaryote itself, thus conception is not achieved until reduction

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to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

An adequate description requires more than a mere statement that it is part of the invention. The specific species of bacterium itself, or a nucleic acid structure is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016. Even where there is an actual reduction to practice, which may demonstrate possession of an embodiment of an invention, it does not necessarily describe what the claimed invention is. Applicants have disclosed the corynebacterial *dtxR* hyper repressor DtxR(E175K) sequence, however applicants have not set forth other sequences encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein.

See also, *In The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), where the court held that a generic statement that defines a genus of nucleic acids by only their functional activity does not provide an adequate description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Thus applicants have not adequately described sequences encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein. Applicants have not disclosed a sequence for a partially metal ion-independent repressor protein.

Thus, in the absence of sequence information of sequences encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein, or other prokaryotes, the composition and virulent or opportunistic prokaryote fails to meet the written description requirements. Therefore only the *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) and not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Deposit Rejection

8. The specification lacks complete deposit information for the deposit of *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K). Because it is not clear that cell lines possessing the properties of the *M. tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) are known and publicly available or can be reproducibly isolated from nature without undue experimentation and because the claims require the use of *M. tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K), a suitable deposit for patent purposes is required. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of the *M. tuberculosis* cell line is an unpredictable event.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has

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authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State. Amendment of the specification to recite the date of deposit and the complete name and full street address of the depository is required.

If the deposit has not been made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR §1.801-1.809, assurances regarding availability and permanency of deposits are required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request;

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application;

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

In addition, a deposit of biological material that is capable of self-replication either directly or indirectly must be viable at the time of deposit and during the term of deposit. Viability may be tested by the depository. The test must conclude only that the deposited material is capable of reproduction. A viability statement for each deposit of a biological material not made under the Budapest Treaty must be filed in the application and must contain:

- 1) The name and address of the depository;
- 2) The name and address of the depositor;
- 3) The date of deposit;
- 4) The identity of the deposit and the accession number given by the depository;
- 5) The date of the viability test;
- 6) The procedures used to obtain a sample if the test is not done by the depository; and
- 7) A statement that the deposit is capable of reproduction.

As a possible means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If the deposit was made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the *M. tuberculosis* cell line described in the specification as filed is the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundack, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR §1.801-1.809 for further information concerning deposit practice.

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9. Claims 1–19 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions of *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K) or a *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K); does not reasonably provide enablement for a composition comprising a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier or a virulent or opportunistic prokaryote. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The specification, at pages 7 and 8 teaches that the preferred prokaryotes are gram positive bacterial species, such as some *Streptococcus* species, *Staphylococcus* species, *Mycobacterium* species, *Actinomyces* species, and only the *Listeria monocytogenes*, *Propionibacterium acnes* and *Erysipelothrix rhusiopathiae* species. Moreover, it is noted that the instant examples are drawn compositions of *Mycobacterium tuberculosis* comprising transformed vector expressing an iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K). The specification fails to teach the identity of other prokaryotes, such as any species of blue-green algae. The specification does not state structural characteristics that a prokaryote would need to qualify as a prokaryote capable of comprising the

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repressor protein. Moreover, there is evidence that other prokaryotic species have not yet been identified and/or classified as capable of comprising the claimed subject matter.

The claims broadly recite a either composition comprising a virulent or opportunistic prokaryote or a virulent or opportunistic prokaryote, in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier. However, neither the claims nor the specification recite other prokaryotes that can be comprised within the claimed composition. The specification teaches only *Mycobacterium* as being comprised within the compositions. Nor does the specification teach recombinant DNA molecules comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein. Therefore, the claims would be enabled for a composition of *Mycobacterium tuberculosis* comprising transformed vector expressing the known sequence for the iron-independent, positive dominant, corynebacterial *dtxR* hyper repressor DtxR(E175K).

Applicants have provided no guidance to enable one of ordinary skill in the art how to make, without undue experimentation, a composition or a virulent or opportunistic prokaryote, comprising a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier. Given the lack of guidance contained in the specification, one of skill in the art could

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not make or use the broad claimed invention without undue experimentation. Thus, one of skill in the art would have to locate de novo steps required for a composition or a prokaryote comprising a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier.

Furthermore, the specification fails to provide an enabling disclosure for composition or prokaryote comprising a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier that meets the limitations of as recited in the claims. Applicants' have provided no guidance to enable one of ordinary skill in the art as to how determine, without undue experimentation, the components of the claimed composition. Given the lack of guidance contained in the specification and the unpredictability for determining such a composition, one skilled in the art could not make or use the broadly claimed invention without undue experimentation.

10. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

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the invention. Acronyms like IdeR and SirR must be spelled out when used for the first time in a chain of claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 1-3, 17, 19 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyd et al.

The claims are drawn to a composition comprising a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier and a virulent or opportunistic prokaryote in which metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein or a partially metal ion-independent repressor protein and a carrier. The dependant claims are drawn to using non-chromosomal vectors, the prokaryote is a bacterium, and that the sequence encode a metal ion-independent, the *dxtR* repressor protein or a partially metal ion independent *IdeR* or *SirR* repressor protein.

Boyd et al., teach molecular cloning and DNA sequence analysis of a diphtheria tox iron-dependant regulatory element (*dtxR*) from *Corynebacterium diphtheriae*. Normally, a family of closely related corynebacteriophages carries the diphtheria toxin, tox; the tox gene products are obtained only when iron becomes the growth rate limiting substrate (abstract). The authors describe the genetic construction of an *E.coli* host strain that carries a diphtheria tox promoter/operator (*toxPO*)-*lacZ* transcriptional fusion in single copy (page 5968). The *E.coli* strains were grown and maintained in the appropriate broths or medium (page 5968). The authors also reported the molecular cloning and amino acid sequence of *dxtR* (page 5968). Therefore a sequence that encodes a DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein, i.e., the *dxtR* repressor protein is taught. See Figure 3 for the nucleotide and amino acid sequence of the *dtxR* gene from *C. diphtheriae* which designates the promoter and ribosome binding sites. The bacterial strains, plasmids and vectors are listed in Table 1. It is noted that the recombinant DNA is contained in non-chromosomal vectors, see the many vectors listed in table 1. Thus the *E.coli* bacterial host strain contained a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor *dxtR* protein.

Thus, Boyd et al., teach a composition comprising a virulent or opportunistic prokaryote is the bacteria *E.coli*, wherein a metal ion-dependant gene regulation confers growth or an infectious advantage, said prokaryote containing a recombinant DNA molecule comprising a promoter in operable association with a sequence encoding a dominant, metal ion-dependent repressor protein, *dxtR*, using non-chromosomal vectors.

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Prior Art

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Dussurget et al., teach transcriptional control of the iron-responsive *fxbA* gene by the Mycobacterium regulator *IdeR*. Schmitt et al., teach characterization of an iron-dependant regulatory protein *IdeR*. Sun et al., teach the isolation and characterization of iron-independent positive dominant mutants of the diphtheria toxin repressor *DtxR*.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ja-Na Hines whose telephone number is 703-305-0487. The examiner can normally be reached on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 703-308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Ja-Na Hines 
October 1, 2003


LYNETTE R. F. SMITH
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